



DEPARTMENT OF HEALTH & HUMAN SERVICES

ms163n
Food and Drug Administration
Rockville MD 20857

CBER-01-011

FEB 8 2001

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Andrew Storey
Vice President, Quality, Clinical and Regulatory Affairs
Cangene Corporation
104 Chancellor Matheson Road
Winnipeg, Manitoba
Canada R3T 5Y3

Dear Mr. Storey:

The Food and Drug Administration (FDA) conducted an inspection September 25 through October 11, 2000, of Cangene Corporation, located at 104 Chancellor Matheson Road, Winnipeg, Manitoba, Canada. During the inspection, the FDA investigator documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) and deviations from the applicable standards and requirements of Title 21, Code of Federal Regulations (CFR), Parts 210-211 and Parts 600-680, as follows:

1. Failure to inform the Food and Drug Administration about each change in the product or quality controls [21 CFR 601.12], in that the specification for HBIG visual examination was changed on March 3, 1999, _____
2. Failure to conduct a thorough investigation of any unexplained discrepancy or failure of a batch to meet its specifications [21 CFR 211.192], in that the investigation of HBIG lots _____ which failed particulate inspection, _____

3. Failure to establish and follow sampling and testing plans in written procedures to include the method of sampling and the number of units per batch to be tested [21 CFR 211.165(c)], in that:
 - a. SOP 4.000.0011.01, entitled "Manual Bulk Product Inspection of Liquid Products in Vials," _____

 - b. SOP 3.001.0058.06, entitled "Automatic Inspection of Liquid Bulk Product Using the _____

4. Failure to validate the following assays that are used in the manufacture of HBIG product [21 CFR 211.165(e)]:

5. Failure to reject products failing to meet established specifications [21 CFR 211.165(f)], in that WinRho and HBIG lots were released although results of the aggregation and fragmentation analyses did not meet specifications.
6. Failure to establish procedures to validate those manufacturing processes that may be responsible for causing variability in characteristics of in-process material and finished product [21 CFR 211.110(a)(3)], _____

7. Failure to establish reliability of supplier's test results through appropriate validation of the supplier's test results at appropriate intervals [21 CFR 211.84(d)(3)], in that stoppers purchased from the supplier have not been confirmed to be _____
8. Failure to determine that equipment is cleaned, maintained, and sanitized at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality or purity or other established requirements [21 CFR 211.67], in that:
 - a. there are no cleaning validation data for tank : _____

- b. cleaning validation of tanks _____ was not successful;
- c. there are no cleaning validation data for _____; and
- d. there was no test performed for residual Inactine after cleaning tank _____ prior to manufacture of HBIG lot _____

We acknowledge receipt of your response, dated November 13, 2000, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our evaluation of your response and requests for further information are detailed below. Please note that our comments are numbered to correspond to the items listed on the Form FDA 483:

- 1. Your response refers to the March 3, 1999, procedural memo, which states that

- 2. The _____, dated March 3, 1999 superseded Cangene SOP 4.000.0011.01, entitled "Manual Inspection of Liquid Products in Vials." Did Cangene's Quality Unit review the change? Was Cangene's change control procedure followed?
- 4C. Please provide the anticipated date of completion of the homogeneity study.
- 6. Your corrective action for dealing with the Eisai ejection of vials due to _____ was to perform the inspection within 21 days of filling. Please be advised that this is not an acceptable corrective action. The root cause should be addressed. Your proposed action of formulation development and stability protocols appears adequate. However, please provide estimated time of completion and approximate date of submission of your Prior Approval Supplement.

- 7A. It appears that you are intending an addendum to the previous WinRho assay method validation to provide rationale for the use of the assay for HBIG products. Please be advised that the _____ should be validated for HBIG using HBIG products.
- 7C. Please explain how retest and failed results will be handled on the release protocols sent to CBER for approval.
8. It appears that you are intending an addendum to the previous WinRho assay method validation to provide rationale for the use of the assay for HBIG products.

_____ should be validated for HBIG using HBIG products.
- 9B. Your response states that “the efficiency of the new column is better” Please describe the new column and state how the new column is better.
- 11A. _____

_____ Please provide the estimated date of completion of this validation.
13. _____

14. Your response appears to be adequate, however, please provide an estimated date by which these corrective actions will be implemented.
16. Please ensure that the study you propose will demonstrate the appropriateness of sites sampled in the class _____ areas.
17. Your response states that one lot of each stopper size and configuration will be tested annually for all licensed products. Please provide the approximate date of completion for the current year’s testing of the _____ Stopper endotoxin level.
20. _____

22. Your response states that controls are being put into place to ensure that required cleaning validations are completed prior to any new compound being introduced into the facility. Please describe these controls.

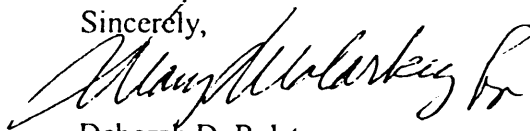
The above violations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as Vice President to assure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the Form FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt measures to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include, but are not limited to, license suspension and/or revocation, seizure and/or injunction.

Please notify this office within 15 days of receipt of this letter, of the specific steps you will take to comply with our request. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HEM-610. If you have any questions regarding this letter, please contact Janet Claggett at (301) 827-6201.

Sincerely,



Deborah D. Ralston
Director
Office of Regional Operations